Chapter

The Brain Stress System in the Neurobiology of the "Dark Side" of Addiction and Its Relation to Neurodegeneration

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Abstract

Addiction is a chronically relapsing disorder characterized by a compulsion to seek and take a substance of abuse, the development of dependence, and a negative emotional state when intake is stopped. Compelling evidence argues that dysregulation of the brain stress system is a key constituent of the addiction process. Through mechanisms of negative reinforcement, the stress system is posited to induce negative emotional state referred to as the 'dark side of addiction' as it becomes the powerful motivation for drug-seeking associated with compulsive use. Therein, the neuropharmacological actions of corticotropin-releasing factor (CRF) is posited to play a key role in the anxiety/stress-like effects of acute withdrawal, anxiety/stress-like effects of abstinence, and relapse to drug taking. In this view, the present chapter sheds a critical light on latest research developments implicating this largely neglected component of substance abuse to give insight into the neuropathology of the 'dark side' of addiction. Moreover, the chapter provides insight into individual vulnerability to addiction and proposes a novel treatment candidate for the disorder.

Keywords: addiction, stress, neurobiology, corticotropin-releasing factor, hypothalamic-pituitary-adrenal (HPA) axis

1. Conceptual framework

DSM-5 defines addiction as an evolving and chronically relapsing disorder, characterized by a compulsion to take drugs, the development of dependence and a motivational withdrawal syndrome with a negative emotional state when access to the drug is prevented [1, 2]. The profound malaise and anxiety during withdrawal, protracted abstinence syndrome marked by a low-level anxiety/dysphoria, and a high vulnerability to relapse upon exposure to an acute stressor is aptly termed 'the dark side' of addiction. It is the common element of the disorder, although all addictions to different drugs are characterized by distinct patterns with emphasis on different stages of the addiction cycle.

The disorder typically progresses in a cyclical manner through three stages, namely preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect (see **Figure 1**). The early stages of the cycle are characterized by impulsivity,

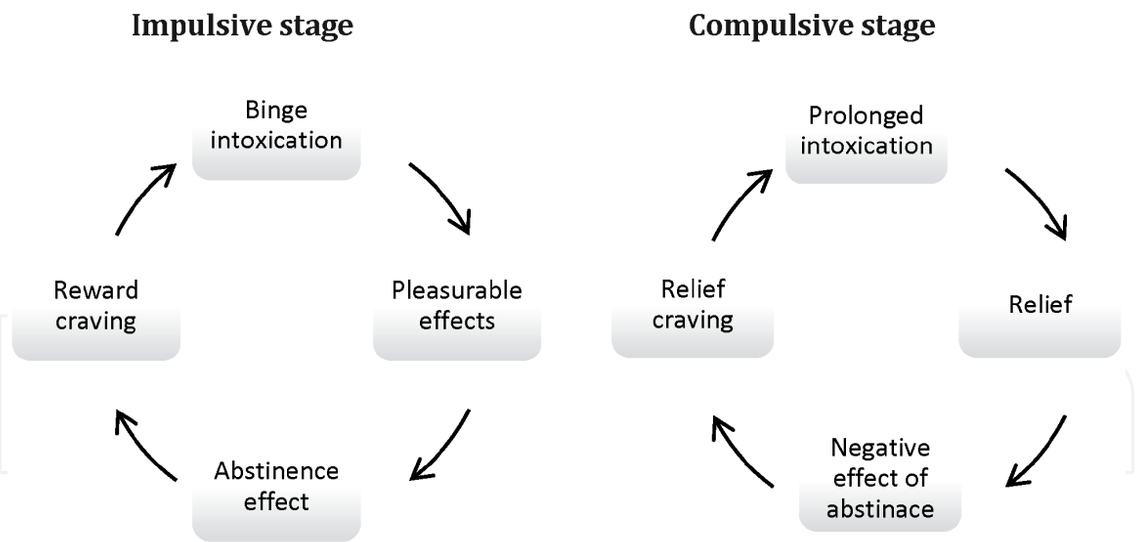

Figure 1.
The progression of alcohol dependence over time marked by a shift in underlying motivational mechanisms. From initial, positively reinforcing, pleasurable drug effects, the addictive process progresses over time to being driven by negatively reinforcing relief from a negative emotional state.

whereas terminal stages are dominated by compulsivity. The former refers to rapid reactions to internal and external factors with no concern about negative outcomes whilst the latter to perseveration in actions despite adverse consequences or in the face of incorrect responses in choice situations. As the cycle of drug taking and withdrawal continues, the different components of the addiction cycle become more intense, and progressively evolve into a more severe pathology [1]. This process is accompanied by changes in the motivational behavioral mechanism that maintains addiction. Inasmuch as removal of negative emotional state associated with drug withdrawal becomes the mechanism driving the dependence-induced drug intake, there is a shift from positive to negative reinforcement maintaining the motivated behavior [3].

2. The dark side of addiction

In relation to the dark side of addiction, a wealth of data supports that symptoms of acute withdrawal from chronic drugs of abuse tend to be affective in nature, persist beyond the acute phase to protracted abstinence, and precede relapse to drug-seeking [4, 5]. Tension, fatigue and anxiety related to alcohol withdrawal have been shown to last from 5 to 9 months post-withdrawal [6, 7]. Furthermore, negative affective symptoms appear to be the leading precipitant of relapse [8, 9]. By way of example, the association between relapse and a subclinical negative affective state was shown to be particularly strong in patients with alcohol dependence, who underwent a 12-week clinical trial [10]. Animal data further shows that a history of dependence lowers the "dependence threshold" and makes the subsequent addiction more severe, relative to subjects receiving alcohol for the first time [11–14]. Moreover, the former category evidenced a prolonged elevation in ethanol self-administration after acute withdrawal and detoxification [15–18], and this was accompanied by increased overt responsivity to stressors and increased responsivity to antagonists of the brain CRF systems [19–21]. Finally, evidence exists to support that a history of prior dependence increases sensitivity to stress-induced reinstatement upon exposure to variety of stressors such as footshock, social stress, or pharmacological stress (e.g., yohimbine) [22]. Notably,

the neural mechanism of stress-induced reinstatement overlaps with that of acute motivational withdrawal [23]. In what follows, next sections of the chapter provide a conceptual framework linking addiction to stress systems.

3. Brain stress systems and addiction

In neural terms, the "dark side" of addiction is posited to be mediated by activation of brain stress system that interacts with hormonal stress systems. Emerging evidence have highlighted that dysregulation of brain arousal/stress systems plays a key role in pathophysiology of drug addiction [2]. More relevant to this chapter, the negative emotional state associated with the dark side of addiction has been linked to a cycle of increasing dysregulation of brain reward/anti-reward mechanisms. Therein, corticotropin releasing factor (CRF) appears to be the prominent component of the negative reinforcement processes that drive the compulsivity of addiction [2].

CRF is a 41-amino acid polypeptide that mobilizes the body's hormonal, autonomic, and behavioral responses to stressors (for a review of the biology of CRF systems see [24, 25]). It has a wide distribution across the brain with particularly high concentrations of cell bodies in the paraventricular nucleus of the hypothalamus, the basal forebrain, and the brainstem [26]. Therein, majority of stress-like effects are mediated by the brain and pituitary CRF_1 receptors [25]. The urocortin/CRF_2 systems have been less explored, with some data pointing to neuroadaptation associated with chronic drug use, also in opposition to the effects of the CRF_1 receptor.

Initial drug use at the binge/intoxication stage of addiction cycle activates the hypothalamic pituitary-adrenal (HPA) axis, which initiates acquisition of drug-seeking behavior through activity in the brain motivational circuits [27–30]. HPA axis activity is characterized by a cascade of physiological changes within the paraventricular nucleus of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland (for review, see Ref. [31]).

The CRF is synthesized by neurosecretory neurons in the medial parvocellular subdivision of the paraventricular nucleus and released into the portal blood vessels of the anterior pituitary gland. Therein it binds to the CRF_1 receptor on pituitary corticotropes triggering the release of adreno-corticotropin hormone (ACTH) into the systemic circulation, which induces glucocorticoid synthesis and secretion from the adrenal cortex.

Once drug-seeking behavior is initiated, the transition from acute to chronic administration of drugs of abuse is mediated by progressive changes in the HPA axis that can lead to subsequent activation of extrahypothalamic brain stress systems characterizing the withdrawal/negative affect stage [32–34]. The HPA axis is regulated via negative feedback from circulating glucocorticoids that act on glucocorticoid receptors in the paraventricular nucleus and the hippocampus. Although high levels of glucocorticoids can feedback to shut off the HPA axis, they can also sensibilize CRF systems in the central nucleus of the amygdala and basolateral amygdala involved in behavioral responses to stressors [35–39]. This observation lends support to the thesis that CRF has a key role in the dark side of the addiction process.

4. Allostatic model of addiction

As the cycle of drug taking and withdrawal continues, the different components of the addiction cycle become more intense, changes also the motivational

behavioral mechanism that maintains addiction. The shift from positive to negative reinforcement behind motivation in compulsive drug use might be explained by allostatic model of the brain motivational systems. It defines addiction as a failure of counteradaptive processes of optimal homeostatic reward functioning to return to their normal range [2, 40]. Therein, the posited mechanism of pathology is mediated by within-system neuroadaptations (changes in reward pathways) and between-system neuroadaptations (brain stress systems) [1, 41].

The body's response to stress related to addiction is controlled by CRF in the paraventricular nucleus of the hypothalamus. It maintains homeostasis by orchestrating rapid and sustained responses to anticipated challenges to normal operating level of the regulatory system. Upon exposure to an environmental challenge, a feed-forward mechanism continuously re-evaluates the environmental demand for adaption, and accordingly readjusts all parameters toward new set points to mobilize resources quickly. However, it might become the engine for pathology if insufficient resources are available to shut off the response. This leads to an allostatic state, defined as a stability with an altered set point [42]. In this view, CRF becomes the key contributor to allostasis and it is hypothesized to mediate the compulsivity and relapse to drug-seeking and drug-taking in addiction [43].

More relevant to this treatise, repeated administration of drugs of abuse leads to an alteration in psychological homeostatic processes, characterized by overactivation of normal arousal or emotional systems in the body [44]. Given that addiction shares some common characteristic with chronic physiological disorders, it allows to speculate that it represents a chronic deviation of the regulatory system from its normal operating level, rather than mere homeostatic dysregulation of emotional function.

Just like any chronic physiological disorder, addiction is subject to significant environmental stressors, deteriorates with time, and is marked by a residual neural trace for rapid re-addiction even after years of abstinence. In response to excessive drug use the brain attempts to maintain homeostatic stability through molecular, cellular, and neurocircuitry changes that occur at the cost of allostatic state. Allostasis represents a chronic deviation from optimal brain emotional regulation marked by decreased function of reward circuits, strengthened stimulus–response associations, loss of executive control and recruitment of the brain stress systems. These neurobiological changes underpin the chronic elevation of reward threshold associated with negative emotional state, thereby contributing to the compulsive drug use [45]. In this view, the cycle of increasing dysregulation of brain reward/anti-reward mechanisms constitutes the posited mechanism of the negative emotions in addiction and compulsive drug use.

5. CRF in the dark side of addiction

All drugs of abuse activate the HPA axis during acquisition of drug-taking and acute withdrawal from the drug by releasing CRF in the paraventricular nucleus of the hypothalamus. Activation of the axis during acute administration facilitates activity in the brain motivational circuits of drug reward, thereby promoting acquisition of drug-seeking behavior [27–30]. Repeated administration dysregulates these acute changes beyond HPA axis to affect the brain extrahypothalamic stress system [46–49]. Therein the repeated exposure to high levels of glucorticoids may have profound effects on the extrahypothalamic brain stress systems, contributing to the persistence and relapse to cycles of addiction to drugs of abuse [32]. Repeated addiction cycles not only blunt the HPA axis response but also sensitize the response of the extrahypothalamic CRF stress system in the amygdala [34]. Whilst initially

the presence of glucocorticoids enhances response to novelty and reward, sensitization of CRF systems in the extended amygdala may contribute to a stress component of the shift from homeostasis to pathophysiology of drug addiction. The stress component is posited to constitute an opponent anti-reward process response to excessive activation of reward systems [2].

Compelling evidence exist to support the thesis that the neuroanatomical substrates for many of the motivational effects associated with the dark side of addiction constitute a common neural circuitry within the basal forebrain, termed the "extended amygdala" [50]. It represents a macrostructure comprising the bed nucleus of the stria terminalis, central medial amygdala, and a transition zone in the posterior part of the medial nucleus accumbens (i.e., posterior shell) [51, 52]. Importantly, the extended amygdala includes dopamine and opioid peptides associated with the positive reinforcing effects of drugs of abuse, and major components of the extrahypothalamic CRF systems associated with negative reinforcement mechanisms [33]. It receives afferent connections from limbic cortices, the hippocampus, basolateral amygdala, midbrain, and lateral hypothalamus and efferent connections to the posterior medial ventral pallidum, ventral tegmental area, various brainstem projections, and to the lateral hypothalamus [52]. The arousal/stress brain systems in the extended amygdala may play a key role in the negative emotional states that maintains addiction to drugs of abuse and may overlap with the negative emotional constituent of other psychopathologies.

6. Brain stress and neurodegeneration

Stress might exert either ameliorating or detrimental effects on physiological processes. In the short term it might be beneficial to an organism however in the long-term it plays a major role in various pathophysiology related to neurodegenerative diseases and mood disorders. Upon exposure to stress the body enters the 'fight or flight' stage, after which it builds resistance to the stress in the adaptation stage, and finally due to 'wear and tear' it reaches exhaustion [53]. In the adaptation stage, cortisol typically exerts a negative feedback effect to shut down the stress response. Multiple brain regions related to cognition are actively involved in feedback regulation including the hippocampus, amygdala, the brain stem and prefrontal cortex [54]. Accordingly, stimulation by corticosteroids induced at the level of the amygdala, the prefrontal cortex and the locus coeruleus was found to interfere with HPA activity and memory [55]. A deficient cortisol feedback effect caused by glucocorticoid resistance increases the activity of the HPA-axis have been found to be associated with neurodegenerative diseases, obesity, heart disease, depression, and a variety of other health issues [56]. Therein the vasopressin neurons of the central nervous system inhibit the regulatory influence of CRH neurons in the PVN resulting in a disproportionally high activity of the HPA system.

Given the inhibitory control of the hippocampus over the HPA-axis, damage to this structure is posited to be causally involved in disinhibition of the HPA axis activity thereby accounting for the age-related accumulation of hippocampal damage in Alzheimer's disease (AD) and depression. This thesis is furthered by evidence of increased cortisol plasma levels in early stage of AD associated with cognitive decline [57], and a correlation of salivary cortisol levels with the severity of the disease [58]. Accordingly, neuronal atrophy was evidenced in the hippocampus of stressed or corticosteroid-treated rodents and primates [59]. Elevated CRH and cortisol levels were also shown to contribute to the symptoms of depression in a large subpopulation of depressed subjects [56]. This is corroborated by the normalizing effect of antidepressants on the synthesis of CRH by stimulation and/or upregulation of

corticosteroid receptor expression, and reversal the clinical symptoms [60]. In light of these evidence, the 'glucocorticoid cascade hypothesis' is posited to be the dominant pathogenetic mechanism in human neurodegenerative diseases marked by HPA-axis alterations including depression and AD [61].

Although CRH and cortisol seem to be etiologically involved in the development of depression, conclusive arguments cannot be drawn due to no evidence for any major damage in the human hippocampus in the disorder. Moreover, reduced hippocampal volume does not necessarily translate in cell death and might alternatively be explained by changes is water content or the structure in glial cells.

7. Summary and conclusions

Addiction to all drugs of abuse involves activation of the HPA axis. Pathophysiology of drug addiction involves dysregulation of the brain emotional system posited to be a key constituent of the negative emotional state produced by dependence that maintains drug-seeking through the mechanism of negative reinforcement. More specifically, the action of CRF in extra hypothalamic systems in the extended amygdala is considered a neural substrate of the pathophysiology of the disorder and plays a key role in maintaining the addiction cycle once it is initiated. It comprises the central nucleus of the amygdala, bed nucleus of the stria terminalis, and a transition area in the shell of the nucleus accumbens. Beyond providing insight into the neurobiology of the dark side of addiction, better characterization of the CRF systems in addiction hold promise for new targets for identifying vulnerability to addiction and novel treatments for the disorder.

Conflict of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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